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ADENOMA OF THE BRONCHUS

HAROLD E. HARRIS, M.D.

Bronchial adenoma is a type of tumor peculiar to the trancheobronchial tree about which controversy has existed for fifteen years. Disagreement among pathologists as to terminology and interpretation of the morphologic picture hinders proper classification and correct management. The great variability in the clinical course of malignant lung tumors in general also helps confuse the issue. Undoubtedly many of these tumors have been classified adenocarcinoma, alveolar carcinoma, and mucous gland carcinoma, the true nature of the lesion not being recognized.

Two widely different opinions exist as to proper management of bronchial adenomas. One group classifies the tumors as benign and treats them by bronchoscopic removal.[1] By the second group they are considered malignant or potentially malignant, and lobectomy or pneumonectomy is recommended.[2]

Because of the tumors' glandlike structure and absence of the usual criteria of malignancy, the term *benign glandular tumor of the bronchus* has been suggested. Ultimately malignancy may be evident by direct extension and involvement of adjacent or distal structures. The term *mixed tumors* is advocated by Womack and Graham,[3] because of the similarity in behavior and origin of this neoplasm to mixed tumors of the parotid gland. They advise regarding the neoplasms as potentially malignant, although many are benign when first recognized.

Incidence. Bronchial adenoma is not uncommon and must be considered in every case of bronchial obstruction. In eighteen months I encountered 5 cases diagnosed histologically as bronchial adenoma. Adenoma is most frequently observed in young women and in the second and third decades of life. Carcinoma, on the other hand, occurs most often in men and after 40.

Symptoms. The symptoms are primarily those of bronchial obstruction and depend upon the tumor's location in the trancheobronchial tree and the degree of obstruction and of inflammation or infection of the lung distal to the lesion. *Chronic cough* is the most common symptom. In 3 patients it was productive and more pronounced at night when the patient was lying down, and in 2 it was nonproductive. In the presence of pulmonary suppuration, the cough is identical with that observed in bronchiectasis. *Hemoptysis*, characterized by sudden onset with massive hemorrhage requiring transfusion, may be the chief symptom and is often severe owing to the pronounced vascularity of these

tumors. *Recurrent pneumonia* with recovery is characteristic, whereas in malignant lung tumors the symptoms are more likely to be progressive. Because of periods of acute pulmonary infection with increased bronchial obstruction, a previous diagnosis of pneumonia is not uncommon. Two patients had an initial diagnosis of pneumonia. Four had a history of frequent pneumonia. Severe *dyspnea* and symptoms of acute laryngotracheobronchitis were the outstanding features in 1 case. All 5 of the reported patients were ill for long periods and previously received treatment for unresolved pneumonia, recurrent acute laryngotracheobronchitis, asthma, and bronchiectasis. Two patients had atelectasis of one or more lobes. In 3 others atelectasis was associated with clinical signs of suppuration. None had emphysema. Because of the tumor's slow growth, extensive fibrosis and bronchiectasis develop. In 1 patient the roentgenogram showed the tumor and evidences of pulmonary disease of many years' duration.

Bronchoscopy. The usual finding is partial or complete occlusion of a bronchus by a smooth reddish or purplish lobulated mass. Small adenomas may appear as a sessile elevation, giving the appearance of an endobronchial tumor. More commonly the bronchial lumen is filled with a large pedunculated mass. The bronchial wall is not fixed or rigid as in carcinoma. Following the course of least resistance, the pedunculated type of tumor tends to grow toward the trachea, so that the proximal portion is movable.

The tumors are usually covered with epithelium, although suppuration may produce superficial erosions. The consistency varies greatly, but softer tumors are usually very vascular and bleed readily with slight trauma.

Pathology. The important question is whether the tumor is benign or malignant, and if benign, whether it will remain benign. All 5 of these patients had polypoid, highly vascular, intrabronchial tumors.

Microscopic examination. The tumor is composed of fairly uniform, polyhedral, cuboidal or low columnar, undifferentiated, epithelial cells held together by abundant stroma. The stroma is fairly vascular and sometimes hyalinized. Mitotic figures are not seen, and necrosis is not present. According to Brunn and Goldman,[4] Jackson and Konzelmann,[5] and others polypoid tumors of the bronchi may be either benign or malignant.

Treatment. Bronchoscopic removal of the endobronchial portion usually reestablishes drainage of the lung distal to the growth and with electrocoagulation may be sufficient to reestablish and maintain an adequate bronchial lumen. The tip of the bronchoscope is very useful for

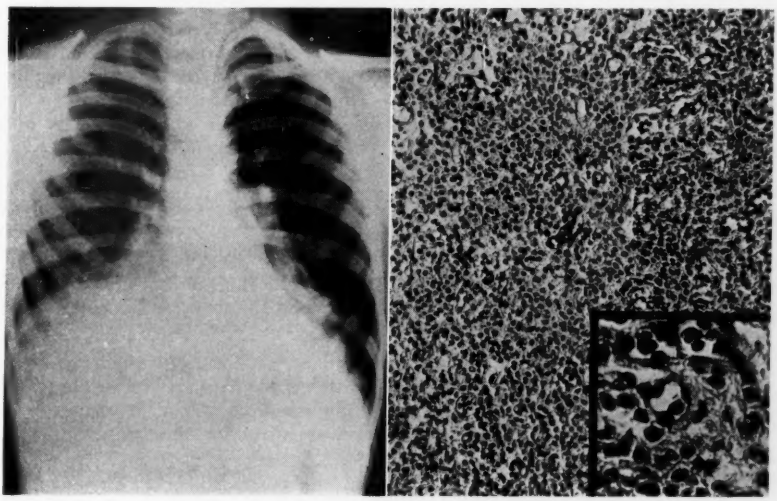
coring out the tumor and scrubbing the bronchial wall to remove remaining particles of tumor. If chronic pulmonary changes with bronchiectasis distal to the tumor have developed, reestablishment of drainage may greatly relieve symptoms, although extirpation of the bronchiectatic portion of the lung is usually indicated.

If compression stenosis of the bronchus is caused by extrabronchial tumor, lobectomy or pneumonectomy is indicated, depending on the location of the lesion. When the tumor is in the upper lobe bronchus and inaccessible to bronchoscopic removal, surgery is indicated.

CASE REPORTS

Case 1—A white boy, aged 12, was admitted to the hospital on September 13, 1943 because of labored breathing, orthopnea, fever, and productive cough. In July of the preceding year he was admitted to a local hospital with a diagnosis of bronchopneumonia and laryngeal stridor necessitating tracheotomy. In November 1942 he was again hospitalized for acute laryngotracheitis for which another tracheotomy was performed. His third admission was in May 1943 when a diagnosis was made of chronic bronchitis, emphysema, obstruction, and possible bronchiectasis. On September 7 he had fever and malaise followed by cough productive of yellow sputum, labored breathing, and orthopnea preceded by abdominal pain.

The boy was thin and pale. Respirations were wheezing and orthopneic. Loud râles and rhonchi were present throughout the chest. Bronchial breathing was present, especially on the left side.



a. *b.*

FIG. 1—Case 1. a. Pronounced infiltration along bronchovascular trunks to both lower lobes. Upper halves of lung fields clear. Appearance suggests advanced bilateral bronchiectasis. b. Masses of small round or polygonal cells with poorly defined cytoplasm and relatively large dark nucleus. Stroma contains goodly number of capillaries filled with blood.

Roentgenogram of the chest showed extensive fibrous and exudative infiltration at the hilus and lower lobe of both lungs, believed to represent bilateral lower lobe bronchiectasis. Clinical impression was bronchiectasis with superimposed bronchial asthma. Sputum culture showed pneumococcus, type 8, and was negative for tuberculosis and fungi.

During hospitalization the patient obtained relief with symptomatic treatment and sulfadiazine and was discharged improved on the tenth hospital day.

He was readmitted on September 26, 1943 with severe dyspnea and apprehension, and a diagnosis of laryngeal or tracheal obstruction with secondary bronchiectasis was made.

Bronchoscopy revealed a reddish pedunculated tumor mass, friable and vascular, almost completely obstructing the lower end of the tracheal lumen and orifice of the left main stem bronchus. A large quantity of mucopus below the level of the lesion was aspirated. Upon removal of the tumor tissue and passage of the bronchoscope beyond the tumor mass, a foreign body (pickle rind) was encountered in the left main stem bronchus. This had been aspirated September 7 at the onset of the present illness.

Bronchoscopy completely relieved the dyspnea. Culture of aspirated bronchial secretions showed nonhemolytic streptococcus. Biopsy report was polypoid adenoma with no evidence of malignancy.

In spite of apparent relief from symptomatic treatment, postural drainage, and sulfadiazine, convalescence was complicated, and the patient died on October 2, 1943 on the sixth hospital day. Permission for necropsy was not granted.

Case 2—A white married woman, aged 43, was seen on July 25, 1944 with a complaint of severe productive cough of seven months' duration and discomfort over the left substernal area and shoulder, which was aggravated by deep breathing. In January she had a severe episode of "flu" from which she apparently recovered. However, coughing persisted and gradually became productive of white mucoid sputum, which later became purulent. She became easily dyspneic and wheezed frequently. Other symptoms were weight loss of 35 pounds, recurrent bouts of chills and fever, generalized aches and pains, and occasional night sweats.

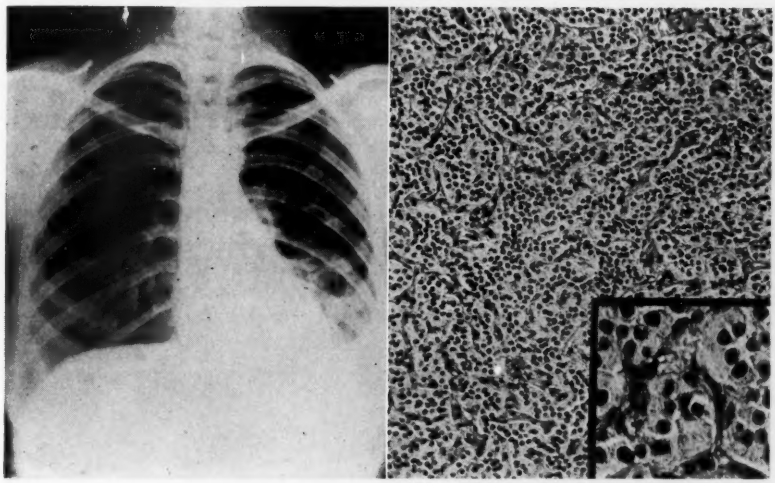
Mobility of the chest was decreased, especially on the left. Percussion note was resonant throughout. Breath sounds were distant. There were a few coarse expiratory rhonchi over both lungs. Clinical impression was lung neoplasm.

Chest roentgenogram showed thickened pleura at the hilus of the left lung and some fibrosis in the upper left lobe indicating an old inflammatory process. Laboratory findings were within normal limits.

Bronchoscopy revealed a round smooth reddish pedunculated tumor mass projecting from the orifice of the left upper lobe bronchus and partially obstructing the left main stem bronchus. Because of its location, the tumor could not be removed completely. There was no bronchoscopic evidence of secondary bronchiectasis.

Pathologic report of tumor tissue removed by bronchoscopy was bronchial adenoma (left upper lobe) with squamous cell metaplasia of the bronchial mucosa. Aspirated bronchial secretions were negative for tuberculosis, spirochetes, and fungi but were loaded with pus.

A total left pneumonectomy was advised and carried out on October 7, 1944 with an uneventful recovery.



a. *b.*

FIG. 2—Case 2. a. Triangular lesion with apex at left hilus close to the mediastinum and fanning out toward apex of lung, where it becomes less distinct. Suggests inflammatory lesion of left upper lobe. b. Closely packed, medium-sized, cuboidal cells subdivided into alveoli and trabeculae by rich sinusoidal circulation. Neoplastic cells intimately related to endothelial wall of vascular sinusoids. No tumor seen within blood vessels.

Case 3—A white housewife, aged 25, was seen on September 11, 1944 with the complaint of intermittent pain in the left lower chest around the entire costal margin and in the left shoulder of approximately two years' duration. In July 1942 she had whooping cough and in November, left lobar pneumonia. Intermittent chest pain persisted as well as a cough with alternately clear and purulent sputum. Hemoptysis of one week's duration occurred initially after a severe coughing spell two months prior to admission. During the summer of 1943 she lost 35 pounds and had intermittent bouts of fever reaching 104 to 105 F. An unconfirmed diagnosis of tuberculosis kept her at bedrest for several months. She was afebrile from August 1943 until a few days prior to admission, when her temperature averaged 100 F. and was associated with recurrent chest pain aggravated by deep breathing and motion. In all she had pneumonia on eight different occasions in the previous eight or nine years.

Her temperature on admission was 98.7 F. There was some decrease in resonance at the base of the left lung and tenderness about the lower angle of the left scapula. A few fine scattered rhonchi were audible over the left chest, and breath sounds were decreased over the left base.

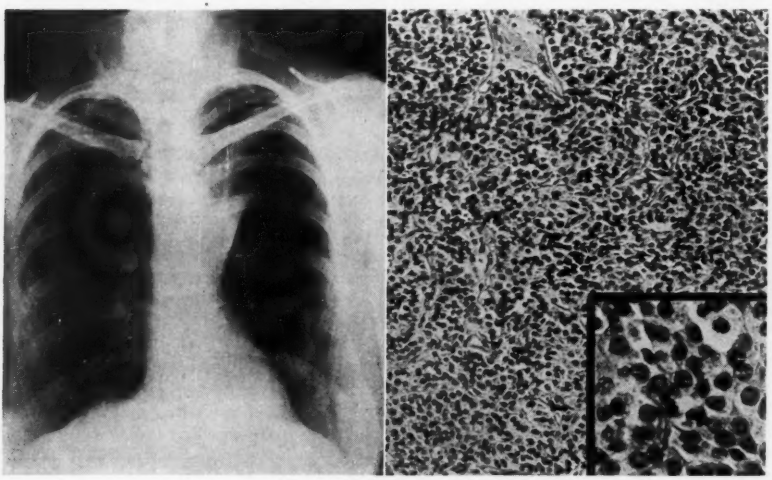
Roentgenogram of the chest revealed evidence of extensive bronchiectasis in the lower left lobe. The upper left lobe and the right lung were clear. Laboratory reports were within normal limits.

Bronchoscopy on September 12, 1944 revealed a purplish smooth round nodular tumor completely obstructing the left lower lobe bronchus and extending up to and partially including the left upper lobe bronchus. Tumor tissue was removed and the left lower lobe bronchus found to be filled with pus.

Pathologic report of tumor tissue removed at bronchoscopy was adenoma of the bronchus (left lower lobe). Aspirated bronchial secretions showed few acid-fast bacilli and a culture of nonhemolytic streptococcus.

The patient was placed on sulfadiazine therapy and postural drainage and upon returning on November 7, 1944 was found to be symptomatically improved, although cough with purulent sputum persisted. Bronchoscopy showed tumor tissue partially obstructing the left lower lobe bronchus, which biopsy revealed to be adenoma with superficial ulceration, acute inflammation, and necrosis. Culture of bronchial aspirations showed many acid-fast bacilli, nonhemolytic streptococcus, and Staphylococcus albus. The pulmonary lesion did not suggest tuberculosis either clinically or roentgenologically.

A left lower lobectomy was advised, but after her last visit to the clinic, she showed personality changes, possibly caused by brain abscess secondary to pulmonary infection. She was admitted to a state hospital where a diagnosis was made of dementia praecox and catatonic excitement. No improvement was reported, and her mental condition remained unchanged.



a. *b.*

Fig. 3—Case 3. a. Group of thin walled cavities in lower two-thirds of left lung. Posterior position of lesions indicates they are in left lower lobe. Appearance suggests severe saccular bronchiectasis. b. Tumor cells uniform in size and shape with abundant acidophilic cytoplasm. Majority are cuboidal and have fairly dark nuclei. No abnormal nuclear forms or mitoses. Connective tissue stroma contains usual cells of inflammation. Many tumor cells surround small clear spaces, resembling well formed glands; others present in parallel columns and groups.

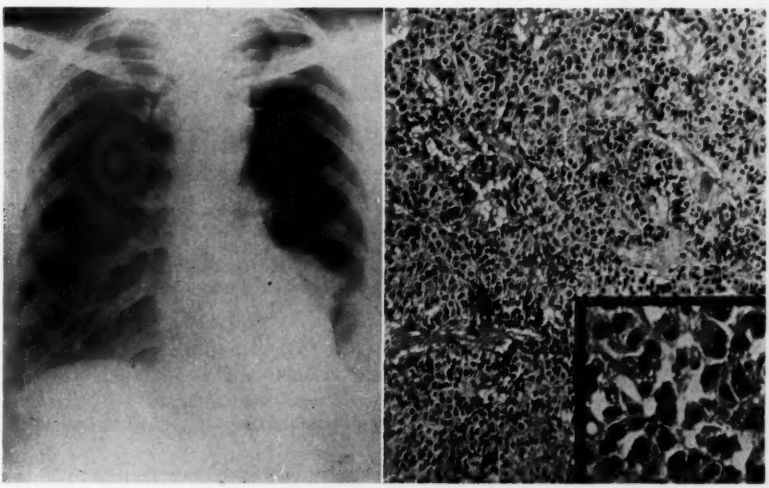
Case 4—A white single woman, aged 20, was seen on October 3, 1944 with a complaint of occasional slight pain in the left chest of approximately ten months' duration. She had two episodes of "flu" the previous winter, after which pleurisy developed in the left chest. Thoracentesis on two occasions was apparently followed by recovery except for the present complaint.

Breath sounds were somewhat decreased in the lower left chest; there was impaired resonance and moderate increase in tactile fremitus, but no clinical evidence of pleural

effusion. Clinical impression was thickened pleura on the left as sequela of postinfluenzal hydrothorax. Roentgenogram of the chest showed thickened pleura and atelectasis of the left lung. The right lung was entirely clear. Laboratory reports were within normal limits.

Bronchoscopy on October 3, 1944 revealed a smooth reddish nodular tumor mass obstructing the left main stem bronchus approximately 1 cm. below the carina. It was found to be attached to the posterior wall, and when removed, profuse bleeding occurred, necessitating packing the bronchus with gauze.

Pathologic report was bronchial adenoma. Aspirated bronchial secretions were negative for tuberculosis, spirochetes, and fungi, but showed nonhemolytic streptococcus and Staph. albus. The remaining tumor was electrocauterized on two subsequent occasions. Bronchoscopy three months later revealed no evidence of tumor, and the patient was symptom free.

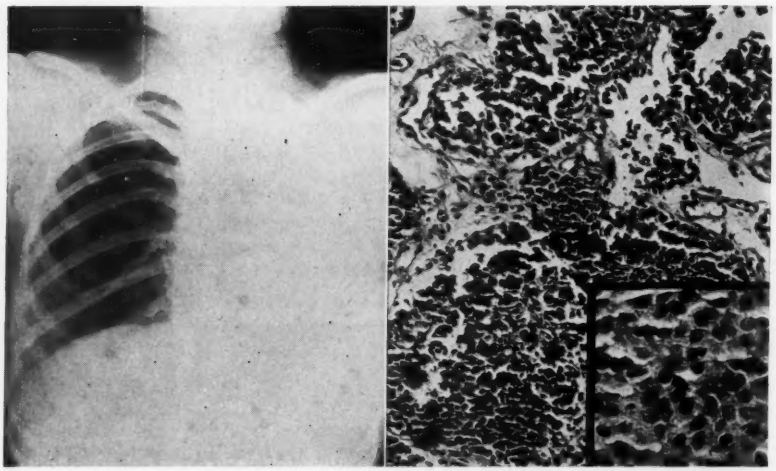


a. *b.*

FIG. 4—Case 4. a. Mediastinal structures displaced far to left. Left lung shadows replaced by homogeneous density. Shadow of left main bronchus can be traced out from carina for approximately 2 cm. where an indefinite tumor mass can be seen, the margin being convex at end of bronchial shadow. b. Highly cellular tumor with uniform type cells. Both circular and oval nuclei are vesicular and moderately chromatic. No abnormal nuclear forms or mitoses. Tumor cells tend to be radially arranged about small vessels or small clear spaces. No well formed glands.

Case 5—A colored housewife, aged 42, was admitted to the hospital on November 5, 1944 for thyroidectomy for nodular goiter without hyperthyroidism. She also complained of a persistent cough after a severe cold approximately eight to nine months before. The nodular goiter was found upon a previous hospital admission on November 19, 1942, when she was treated for pelvic inflammatory disease.

Physical examination revealed nodular bilateral enlargement of the thyroid, particularly the right lobe. The temperature was 98 F., pulse rate 110 per minute, and blood pressure in millimeters of mercury 174 systolic and 96 diastolic. Examination of the



a. *b.*

Fig. 5—Case 5. a. Heart displaced slightly to left. Convex margin of dense lesion, which stereoscopically is posterior to heart and extends about 2 or 3 cm. beyond left ventricle. This nodular lesion suggests a well circumscribed tumor. b. In a partly hyalinized matrix of fibrous connective tissue are masses and anastomosing bands of epithelial cells with clear cytoplasm and circular nucleus. No mitoses seen. Occasional pseudoacinic structure and a few well formed acini.

chest was negative. Clinical impression was nodular goiter without hyperthyroidism, benign essential hypertension, and mild obesity.

Roentgenologic examination revealed a nodular lesion in the left lung extending out from the mediastinum and some fibrosis in the right lower lobe. The basal metabolic rate was plus 2.

Bronchoscopy on November 8, 1944 revealed a smooth reddish rounded tumor mass obstructing the left lower lobe bronchus. Profuse bleeding followed removal, and the area was electrocauterized on three subsequent occasions. No evidence of tumor remained on the last examination on March 19, 1945. Pathologic report of tissue removed was bronchial adenoma.

SUMMARY

Bronchial adenoma is not an uncommon cause of bronchial obstruction and should be suspected with recurrent symptoms of bronchial obstruction in young or middle-aged women. A correct diagnosis can be made only after bronchoscopy and removal of adequate tissue for microscopic study, since bronchoscopy alone cannot determine the extent of tumor outside the bronchial wall. These tumors are usually benign but tend to recur locally. If accessible to the bronchoscope, they can be successfully destroyed by electrocautery; if inaccessible or peribronchial, lobectomy or pneumonectomy is advisable.

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MASSIVE DOSES OF PENICILLIN IN THE TREATMENT OF PERITONITIS*

A Preliminary Report

GEORGE CRILE, Jr., Lt. Commander (MC) USNR

The purpose of this report is to call attention to the fact that large doses of penicillin (100,000 units or more intramuscularly every two hours) exert a striking effect in controlling peritonitis arising from mixed flora of the intestinal tract. Penicillin, first in large doses and then in diminishing amounts for a week or ten days, will profoundly inhibit dissemination of peritonitis and will result in spontaneous resolution of many intraperitoneal abscesses. Large initial doses of penicillin and protracted therapy produce results far superior to those observed with the usual doses or the sulfonamides.

Early reports on the use of penicillin in peritonitis were equivocal and gave little promise that this drug would be superior to the sulfonamides.[1] At that time penicillin was scarce and expensive, and the average dose was not more than 30,000 units intramuscularly every three or four hours. Penicillin in these doses exerted a striking effect in controlling peritonitis from hemolytic streptococcal or staphylococcal infections, but appeared to do little to control mixed infections from perforated appendixes. Although peritonitis seemed less likely to spread and the patients were less sick, penicillin exhibited little advantage over the sulfonamides. Formation of intraabdominal abscesses was not prevented, and a prolonged febrile course with eventual suppurative complications was the rule.

During the past four months 30 patients with established peritonitis or with extensive contamination of the peritoneal cavity from rupture of intraabdominal abscesses were treated at the U. S. Naval Hospital, San Diego. There were 2 cases of spontaneous perforation of carcinoma

*The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

of the sigmoid, 1 of perforated diverticulitis of the sigmoid, 1 of peptic ulcer perforating into the free peritoneal cavity more than twenty-four hours before operation, 6 of perforated appendixes of from thirty-six hours to five days' duration and not operated upon, and 20 in which perforation of the appendix into the free peritoneal cavity was found at operation or in which a periappendiceal abscess ruptured during removal of an acutely inflamed appendix. Not included in this group was peritonitis from simple perforated ulcers or slight contamination incident to removal of an acutely inflamed appendix.

In none of these cases did intraperitoneal complication occur. Masses, when present, resolved spontaneously without drainage. After five days of treatment the temperature and pulse rate usually fell to normal and remained so. In this series the only complication was wound infection in 5 cases. It is interesting to note that these infections appeared late and were attended by only the mildest systemic reaction and practically no cellulitis.

In this study it soon became apparent that an initial large dose of penicillin maintained until the temperature was normal was not sufficient to control the infection permanently. If penicillin was withdrawn too soon, symptoms and signs of localized intraperitoneal suppuration recurred. In such cases resumption of full doses again controlled the infection and ultimately resulted in a permanent cure.

To prevent these relapses and still to economize as much as possible on penicillin, the dosage was decreased by one-half every two days. For the first two days 100,000 units was given intramuscularly every two hours, then 50,000 units every two hours for two days, 50,000 units every four hours for two days, and finally 25,000 units every four hours for two days, a total of 4,500,000 units in eight days. In 2 cases recurrence of signs and symptoms or development of localized abscess on decreased doses necessitated resumption of full doses for a few days.

The action of large doses of penicillin in controlling mixed infections which did not respond to usual doses is not clear. Cultures of pus at the time of operation have repeatedly shown Bacillus coli and other penicillin-resistant organisms, and usually in addition penicillin-sensitive gram-positive cocci. One interpretation of these observations and of the fact that wound infections are not always controlled, whereas intraperitoneal infections usually are, is as follows:

1. Usual doses of penicillin are not sufficient to overcome the penicillinase (anti-penicillin) effect of the B. coli.[2]

2. When larger doses are given, the penicillinase effect is overcome, and penicillin, although it does not inhibit the penicillin-resistant B. coli, becomes effective against the virulent gram-positive cocci.

3. B. coli and the majority of penicillin-resistant organisms are not virulent or invasive and are essentially saprophytes.

4. Tissues with high resistance, such as the peritoneum, are able to defend themselves against such organisms as B. coli if infection with virulent gram-positive cocci is controlled.

5. Areas of low resistance, such as a wound of the abdominal wall, are not equipped with the defense mechanism of the peritoneum, and saprophytic organisms resistant to penicillin are likely to gain a foothold in dead spaces, in exudate, or in devitalized tissue.

The effect of penicillin on fever is not so dramatic as that observed when a sulfa-sensitive infection is treated with a sulfonamide. Two or three days may elapse before the fever begins to subside, but the pulse tends to remain slow, abdominal tenderness disappears within forty-eight hours, distention is minimized, and the patient looks and feels remarkably well.

Without untoward effects 100,000 units of penicillin has been given every two hours for as long as six days. In fact, the upper limit of the safe dose of penicillin has probably never been reached. In 3 cases of this series hives developed, and in 4 cases fever as high as 102 F. was apparently associated with the administration of penicillin. As soon as the drug was withdrawn, the temperature fell to normal.

SUMMARY

1. Massive doses of penicillin exert a striking effect on peritonitis and, if maintained for a considerable period of time, will usually effect a resolution of intraperitoneal inflammatory masses.

2. Thirty patients with established peritonitis, intraabdominal inflammatory masses, or extensive contamination of the peritoneal cavity from ruptured abscesses were treated with 100,000 units of penicillin every two hours intramuscularly for two days and with diminishing doses for six more days. None developed intraperitoneal abscess or complications.

3. If symptoms and signs of intraperitoneal inflammation recur after the first course of treatment, a second course will probably again control the infection.

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PREMENARCHAL CLIMACTERIC

E. PERRY McCULLAGH, M.D., AND ROBERT H. BECK, M.D.

When climacteric symptoms occur in women, they usually appear between the ages of 40 and 50. They are occasionally seen in women past 60, are quite uncommon before 30 and rare before 20. In almost all cases climacteric symptoms are antedated by relatively normal menstrual periods.

Climacteric symptoms appearing before the menarche are very rare. Albright[1] has used the term *premenarchal menopause praecox* in referring to cases of primary amenorrhea with little or no breast development and persistently positive tests for urinary gonadotrophins. However, similar cases which we have encountered and patients with primary amenorrhea in general do not have menopausal symptoms. In the case reported here climacteric symptoms appeared before the onset of the menses and at an age when puberal changes are not ordinarily complete. In addition to the primary amenorrhea there were typical signs of moderately severe prepuberal primary ovarian deficiency.

CASE REPORT

An unmarried white woman, aged 21, was seen on October 29, 1942 with the complaint of frontal headache of fifteen years' duration. The headaches occurred almost every day over periods of two to three weeks. They were never bilateral but were associated with nausea. Mild diplopia was present but was associated with close work only.

The patient had never menstruated. Since the age of 15 she had experienced hot flashes typical of ovarian deficiency, which spread upward over the neck and head and lasted a few minutes several times daily. They were always more pronounced when she was under nervous tension or had a headache. Libido was minimal. She was extremely emotional and irritable and had poor endurance. There were no other symptoms of pituitary or hypothalamic dysfunction.

The family history was irrelevant. She had occasional attacks of tonsillitis and had mumps at the age of 8.

Physical examination revealed the following significant findings:

Weight—114 pounds (51.8 kg.)
Height—66¼ inches (165.6 cm.)
Span (arms extended)—68¾ inches (171.8 cm.)
Symphysial height—36¼ inches (90.6 cm.)

The hair on the arms and forearms and the axillary and pubic hair was finer and straighter than usual but approximated normal in amount. No breast tissue was palpable, and the nipples and areolae were pale and infantile. The labia were flat and underdeveloped. The vagina admitted one finger, and the vaginal wall showed only slight rugosity. By palpation the uterus was estimated to be one-third normal size.

Stained vaginal smear was typical of severe follicular deficiency. The vaginal cells were chiefly rounded and relatively small. There were very few leukocytes. The smear did not show purely round deep cells as is typical of castrate smears.

The blood count was normal except for 78 per cent (12 Gm.) hemoglobin. Blood cholesterol was 124 mg. per 100 cc., and blood calcium 10.5 mg. per 100 cc. Basal metabolic rate was plus 2. The curve of a single dose 100 Gm. oral glucose tolerance test was as follows:

Hours	Fasting	½	1	2	3	4
Blood sugar (mg./100 cc.)	110	127	48	48	41	74
Urine sugar	0		0		0	

In spite of this evidence no symptoms of hypoglycemia were noted. Urinalysis was normal, and Wassermann reaction of the blood was negative.

Roentgenographic studies of the skull revealed a normal sella turcica with some demineralization of the bone. Epiphyseal age was calculated to be about 20 years, the epiphyseal line at the distal ends of the radius having failed to close completely.

The optic fundi were normal. In the visual field examination the patient called green "pink." The visual field for red was severely constricted.

Bioassay for gonadotrophic hormone in a 24 hour urine specimen showed average rat ovarian weight of 83 mg. and average uterine weight of 78 mg. as compared with an average ovarian weight in uninjected controls of 18 mg. and average uterine weight of 21 mg. Urinary 17-ketosteroid determination done on an unfractionated extract showed 6.2 mg. per 24 hours. Estrogen assay showed less than 10 rat units per 24 hours.

On November 11, 1942 the patient was started on 1 mg. daily of stilbestrol dipropionate orally in courses of twenty-five days. After two weeks of therapy she felt well, was more energetic, and had no headaches. She complained of some soreness of the nipples, and her breasts were noticeably larger. On the twenty-eighth and twenty-ninth days of treatment intramuscular injections of progesterone in doses of 5 mg. were given. Four days after withdrawal of therapy the patient had her first menstrual flow, which was scant and lasted for two days. Further treatment with subsequent uterine bleeding is shown in the treatment schedule and in figure 1.

GONADOTROPHIC HORMONE ASSAYS

Rat Test

Test Animals	BEFORE TREATMENT	AFTER TREATMENT	
	12-1-42	10-21-43	1-18-44
	mg.	mg.	mg.
Ovarian weight. . . .	83	16	19
Uterine weight. . . .	73	19	11
Uninjected Control Animals			
Ovarian weight. . . .	18	26	19
Uterine weight. . . .	21	38	26

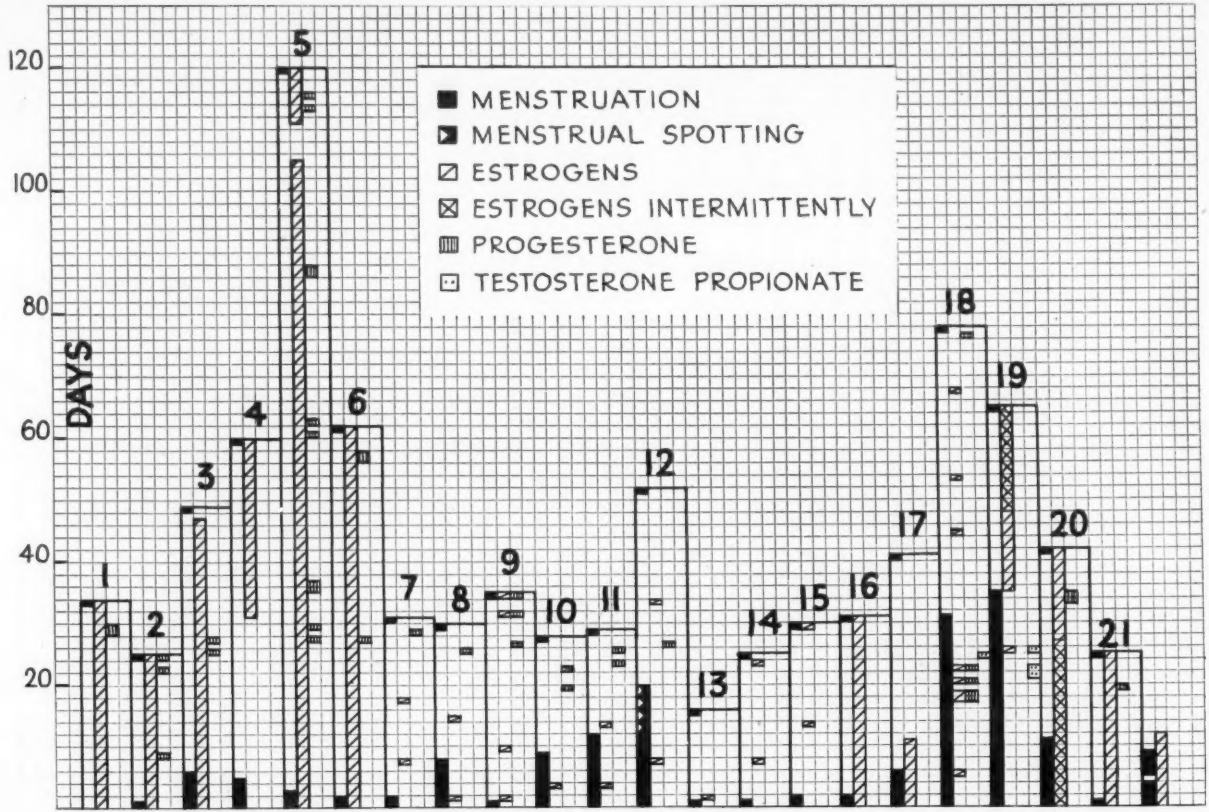


FIG. 1. Menstrual cycles are represented by numbered columns. The solid block at the top of each column represents onset of uterine bleeding, which is continued at the bottom of the succeeding column. Columns 5 and 6 are represented as one cycle, although attempts were made more than once in the interval to incite uterine bleeding.

uterine bleeding, which is continued at the bottom of the succeeding column. Columns 3 and 5 [illegible] attempts were made more than once in the interval to incite uterine bleeding.

TREATMENT SCHEDULE

Cycle	Date	Medication	Daily dose	Route of administration	Duration days	RESPONSE: Vaginal smear	RESPONSE:
1	11–11–42	Stilbestrol dipropionate	1 mg.	Oral	13	4 plus	No headaches or hot flashes. Rested and energetic
	11–24–42	Stilbestrol dipropionate	1 mg.	Oral	22		Good energy. Breasts enlarging.
	12– 9–42	Progesterone	5 mg.	I.M.			
	12–10–42	Progesterone	5 mg.	I.M.			
	12–14–42						
2	12–16–42	Stilbestrol dipropionate	1 mg.	Oral	7		Headaches last only 2 hr. now. Hair coarser. Breasts correspond with puberal development of 12 yr. Nipples are growing. Axillary and pubic hair increasing. Vagina is larger, a speculum can now be inserted. Uterine length 6 cm.
	12–23–42	Stilbestrol dipropionate	2 mg.	Oral	14	Almost 4 plus	
		Estradiol benzoate	2000R.U.	I.M.			
	1– 6–43	Stilbestrol dipropionate	3 mg.	Oral	15	4 plus	No headaches. Feels fine.
		Progesterone	5 mg.	I.M.			
	1– 8–43	Progesterone	5 mg.	I.M.			
3	1–21–43	Stilbestrol dipropionate	3 mg.	Oral	13	About 4 plus	Breasts larger. Axillary and pubic hair more profuse. Vagina larger with more rugosity.
		Estradiol benzoate	2000R.U.	I.M.			
	2– 3–43	Stilbestrol dipropionate	3 mg.	Oral	21	Under 4 plus	
		Progesterone	5 mg.	I.M.			
	2– 5–43	Progesterone	5 mg.	I.M.			
	2–26–43						
4	3–30–43	Patient has not received medication for 34 days. Has felt let down. Frequent headaches and bowel movements. Vaginal smear castrate with some red blood cells.					
	3–30–43	Ethinyl estradiol	0.20 mg.	Oral	13		
		Estradiol benzoate	2000R.U.	I.M.			
	4–12–43	Ethinyl estradiol	0.20 mg.	Oral	10	3-4 plus	Feels quite well.
	4–22–43	Ethyl hexane	15 mg.	Oral	9	3 plus	No nausea. Has a headache.
	4–26–43						
5	5– 1–43	Ethyl hexane	15 mg.	Oral	12		Feels fine.
	5–12–43	Ethyl hexane	15 mg.	Oral	9	4 plus	Severe headaches.
	5–22–43	Ethyl hexane	15 mg.	Oral	11	2-3 plus	Feels headachy and miserable.
	5–25–43	Progesterone	5 mg.	I.M.			
	5–27–43	Progesterone	5 mg.	I.M.			

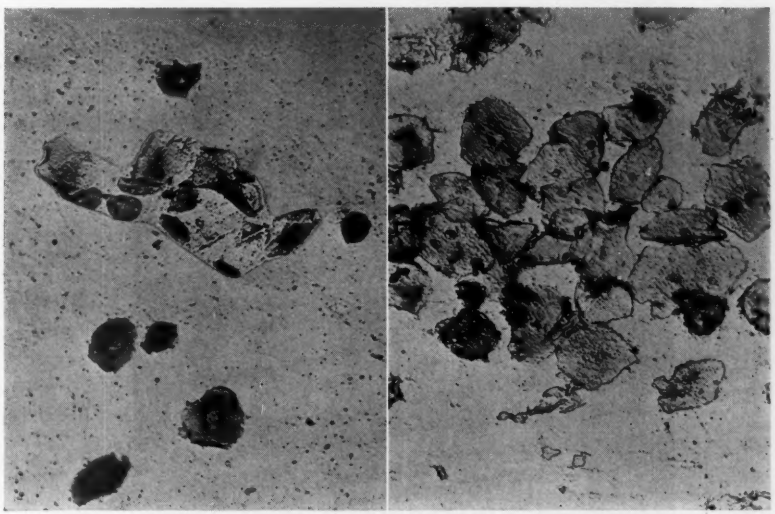
Cycle	Date	Medication	Daily dose	Route of administration	Duration days	RESPONSE: Vaginal smear	RESPONSE:
5	6– 2–43	Estradiol benzoate	2000R.U.	I.M.			Much gastrointestinal disturbance.
		Progesterone	5 mg.	I.M.			
		Monomethyl stilbestrol	10 mg.	Oral	16		
	6– 3–43	Estradiol benzoate	2000R.U.	I.M.			
		Progesterone	5 mg.	I.M.			
	6–18–43	Ethyl hexane	15 mg.	Oral	8	3 plus	
	6–26–43	Ethyl hexane	20 mg.	Oral	20	3 plus	Feels fine.
		Progesterone	5 mg.	I.M.			
	6–28–43	Progesterone	5 mg.	I.M.			
	7–16–43	Ethyl hexane	30 mg.	Oral	8		
	7–22–43	Progesterone	5 mg.	I.M.			
	7–23–43	Progesterone	5 mg.	I.M.			
	7–24–43	Monomethyl stilbestrol	18 mg.	Oral	16	3-4 plus	
	8–16–43	Ethyl hexane	30 mg.	Oral	5	3 plus	
	8–19–43	Progesterone	5 mg.	I.M.			
	8–21–43	Progesterone	5 mg.	I.M.		2 plus	Headaches and hot flashes.
		Monomethyl stilbestrol	18 mg.	Oral	18		
	8–25–43						
6	9– 8–43	Stilbestrol dipropionate	1 mg.	Oral	14	2-3 plus	Feels fine. Few headaches. No hot flashes.
		Estradiol benzoate	2000R.U.	I.M.			
	9–22–43	Stilbestrol dipropionate	2 mg.	Oral	13	2 plus	Feels fine.
		Progesterone	5 mg.	I.M.			
	10– 5–43	Stilbestrol dipropionate	3 mg.	Oral	16	Premenstrual type	Occasional headaches. Feels fine generally.
	10–21–43	Stilbestrol dipropionate	3 mg.	Oral	12	4 plus	Occasional headaches. Feels fine.
		Progesterone	5 mg.	I.M.			
	10–22–43	Progesterone	5 mg.	I.M.			
	10–25–43						
7	11– 2–43	Stilbestrol dipalmitate	5 mg.	I.M.		2-3 plus	10 days later, feels fine, symptom free.
	11–12–43	Stilbestrol dipalmitate	5 mg.	I.M.		4 plus	11 days later, feels fine.
	11–23–43	Progesterone	10 mg.	I.M.			
	11–25–43						
8	11–27–43	Stilbestrol dipalmitate	5 mg.	I.M.			
	12–10–43	Stilbestrol dipalmitate	5 mg.	I.M.			
	12–21–43	Progesterone	10 mg.	I.M.			
	12–25–43						
9	12–27–43	Stilbestrol dipalmitate	5 mg.	I.M.		3 plus	8 days later, looks and feels well.
	1– 4–44	Stilbestrol dipalmitate	5 mg.	I.M.			5 days later, headaches.
	1–21–44	Progesterone	10 mg.	I.M.			
	1–26–44	Estradiol benzoate	4000R.U.	I.M.			
		Progesterone	5 mg.	I.M.			
	1–29–44	Estradiol benzoate	4000R.U.	I.M.			
		Progesterone	5 mg.	I.M.			

TREATMENT SCHEDULE—Continued

Cycle	Date	Medication	Daily dose	Route of administration	Duration days	RESPONSE: Vaginal smear	RESPONSE:	Cycle	Date	Medication	Daily dose	Route of administration	Duration days	RESPONSE: Vaginal smear	RESPONSE:
10	2- 2-44	Stilbestrol dipalmitate.	10 mg.	I.M.		3 plus	16 days later, feels fine.	18	10-28-44	Estradiol benzoate....	6000R.U.	I.M.			
	2-18-44	Progesterone.....	5 mg.	I.M.						Progesterone.....	10 mg.	I.M.			
	2-21-44	Progesterone.....	5 mg.	I.M.			7 days later, feels miserable. Nervous, headaches, cramps.		10-30-44	Estradiol benzoate....	6000R.U.	I.M.			
										Progesterone.....	10 mg.	I.M.			
	2-26-44								11- 1-44	Testosterone propionate.....	50 mg.	I.M.			After bleeding a month, stopped on 11-4-44.
11	3- 1-44	Stilbestrol dipalmitate.	10 mg.	I.M.		About 3 plus			11-21-44	Stilbestrol dipalmitate.	20 mg.	I.M.		2-3 plus	9 days later, headaches returned, irritable. No hot flashes.
	3-11-44	Monomethyl stilbestrol	12.5 mg.	I.M.		4 days later									
	3-21-44	Progesterone.....	10 mg.	I.M.					11-30-44	Stilbestrol dipalmitate.	10 mg.	I.M.		3 plus	14 days later, feels better, fewer headaches.
	3-23-44	Progesterone.....	10 mg.	I.M.											
	3-26-44								12-14-44	Stilbestrol dipalmitate.	10 mg.	I.M.			
12	4- 3-44	Monomethyl stilbestrol	25 mg.	I.M.		2 plus 19 days later			12-23-44	Progesterone.....	10 mg.	I.M.			
	4-22-44	Progesterone.....	10 mg.	I.M.		2-3 plus 22 days later			12-24-44						
	4-29-44	Monomethyl stilbestrol	25 mg.	I.M.				19	1-15-45	Testosterone propionate.....	25 mg.	I.M.			
	5-17-44								1-16-45	Testosterone propionate.....	25 mg.	I.M.			
13	5-19-44	Monomethyl stilbestrol	30 mg.	I.M.			17 days later, headaches for 2 days before bleeding.		1-19-45	Testosterous propionate.....	25 mg.	I.M.			
										Estradiol benzoate....	1000R.U.	I.M.			
	6- 2-44								1-29-45	Monomethyl stilbestrol	25 mg.	I.M.		3 plus	
14	6-10-44	Monomethyl stilbestrol	20 mg.	I.M.						Diethyl stilbestrol....	2 mg.	Oral		12 days later	
	6-26-44	Monomethyl stilbestrol	50 mg.	I.M.		Blood	15 days ater, feels fine. No headaches or hot flashes.		2-10-45	Diethyl stilbestrol....	2 mg.	Oral	Irregularly for 43 days	2-3 plus	44 days later, feeling fine. No headaches or hot flashes. Uterus still not normal size.
	6-27-44								2-27-45						
15	7-11-44	Monomethyl stilbestrol	25 mg.	I.M.		3 plus 10 days later		20	3-26-45	Diethyl stilbestrol....	2 mg.	Oral	30	2-3 plus	No headaches or hot flashes.
	7-27-44	Ethinyl estradiol.....	0.05 mg.	Oral	49	2-3 plus	Head aches and nervous. No hot flashes.		4- 2-45	Estradiol benzoate....	6000R.U.	I.M.			
16										Progesterone.....	5 mg.	I.M.			
	8-27-44									Stilbestrol unguent...	2 mg.	Topical	(appli	ed to bre	asts daily)
17	9- 7-44	Stilbestrol dipalmitate.	15 mg.	I.M.		Severely deficient	36 days later, head aches and nervous. No hot flashes. Uterus larger.		4- 3-45	Estradiol benzoate....	6000R.U.	I.M.			
										Progesterone.....	5 mg.	I.M.			
	10- 7-44								4-10-45						
18	10-13-44	Stilbestrol dipalmitate.	15 mg.	I.M.				21	4-25-45	Diethyl stilbestrol....	2 mg.	Oral	21	3 plus	Headaches and hot flashes recently.
	10-25-44	Estradiol benzoate....	2000R.U.	I.M.					4-30-45	Estradiol benzoate....	6000R.U.				
		Progesterone.....	10 mg.	I.M.						Progesterone.....	5 mg.				
	10-26-44	Estradiol benzoate....	2000R.U.	I.M.					5- 5-45						
		Progesterone.....	10 mg.	I.M.					5-17-45	Hydroxy-phenyl hexane.....	9 mg.	Oral	18		

COMMENT

Anatomic changes were relatively rapid at first but later were less noticeable, although doses of estrogens were larger. After two months of treatment she had no hot flashes and only occasional headaches, which were very mild and lasted not more than an hour or two. Her irritability disappeared, energy and endurance increased, and she gained 15 pounds. Breast size became average normal for approximately 11 to 12 years of age, and the nipples enlarged and darkened. There was some increase in axillary and pubic hair. The vagina had developed, and a slight discharge was present. An almost complete estrogenic response was demonstrated by the vaginal smear (fig. 2a and b). A speculum could be inserted, and the uterine canal measured 6 cm.

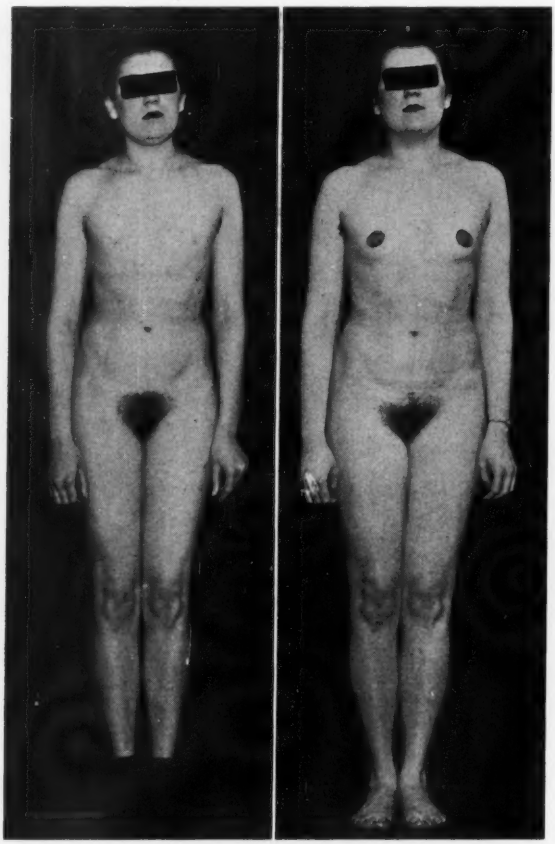


a. *b.*

FIG. 2. a. Vaginal smear before treatment. b. Relatively complete vaginal smear response (Jan. 21, 1943). (x 125)

After over thirty months of treatment little anatomic change appeared to be taking place (fig. 3a and b). The patient usually felt in the best of health, was cheerful, energetic, and free from symptoms except for slight headache, which usually occurred before a period of bleeding. The breasts were 9 cm. in diameter and could be called normal for age 13. The nipples were small, and the nipples and areolae became very

dark brown. Axillary and pubic hair was normal in amount but straighter than average. The labia were underdeveloped, and the clitoris was very small. The vagina was normal in size, the cervix small normal; the fundus was normal on palpation; and the uterine canal measured over 7 cm. in length. Recently an endometrial biopsy on the first day of menstrual bleeding showed a somewhat atypical proliferative (follicular) type of endometrium consistent with changes usually seen early in the cycle.



a. *b.*

FIG. 3. a. Nov. 11, 1942. Relatively normal amount of pubic hair. b. April 2, 1945. Note increase in size of breasts and increase in size and color of areolae.

A considerable array of various estrogens was used in therapy. All were effective, but the dose range varied greatly. The most active from the standpoint of dosage was ethinyl estradiol. This drug given orally in doses of 0.20 mg. daily gave complete symptomatic control and almost a full estrogenic vaginal response. Diethyl stilbestrol in doses of 2.0 mg. per day gave complete symptomatic response but 3.0 mg. was required daily to produce normal vaginal smears. Stilbestrol dipropionate orally in doses of 1.0 mg. a day gave complete symptomatic and vaginal response during the first few weeks. This was not tried later. The dose requirement of all estrogens appeared to rise somewhat during the course of treatment. Ethyl hexane (2,4-di-[parahydroxyphenyl]-3-ethyl hexane) (Benzestrol, formerly Octofollin) gave complete symptomatic response with 20 mg. daily doses, but vaginal smear response was incomplete on a dose of 30 mg. Complete symptomatic response was obtained with hydroxy-phenyl hexane (Hexestrol) with 9.0 mg. per day. Monomethyl stilbestrol ($\alpha\alpha$ diethyl 4 hydroxy 4 methoxystilbene) (Monomestrol) was given intramuscularly on four occasions in doses of 25, 25, 30, and 50 mg. Symptoms recurred in about two weeks after each injection, at which times the vaginal smears were deficient. Intramuscular injections of 5 to 10 mg. of stilbestrol dipalmitate controlled symptoms for more than eleven and more than sixteen days respectively associated with almost complete control of the vaginal smears.

By using moderate doses of estrogen followed by small doses of progesterone and withdrawal, uterine bleeding was brought about repeatedly at intervals which were usually predicted with only fair accuracy. The greatest tendency for bleeding to occur during estrogen therapy and for it to be unduly prolonged followed relatively large injections (15 to 20 mg.) of stilbestrol dipalmitate or monomethyl stilbestrol.

SUMMARY

A case of prepuberal primary ovarian failure with climacteric symptoms is reported. The response of the patient to treatment has been outlined for a period of over thirty months, and some of the observations as to relative effectiveness of various estrogens noted.

REFERENCES

1. Albright, F., Smith, P., and Fraser, R.: A syndrome characterized by primary ovarian insufficiency and decreased stature. Am. J. M. Sc. **204**:625 (November) 1942.

CYSTIC FIBROSIS OF THE PANCREAS

Report of a Case

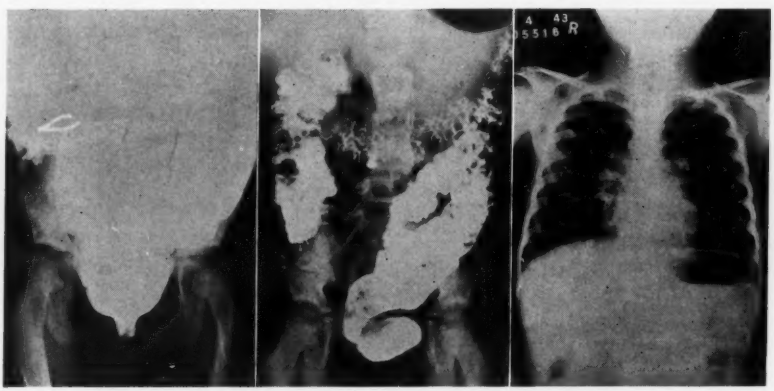
R. M. KISKADDON, M.D., E. N. COLLINS, M.D., AND R. J. F. RENSHAW, M.D.

Cystic fibrosis of the pancreas is a fatal disease of infants and children characterized by a familial tendency, the celiac syndrome, and atypical bronchopneumonia. Prior to 1938 cystic fibrosis was confused with celiac disease but is now known to be one of a number of conditions which produce the symptom complex of the celiac syndrome. This case is reported because of the rareness of the condition.

CASE REPORT

A schoolgirl, aged 9, was admitted to the Cleveland Clinic Hospital on September 27, 1943.

She was hospitalized elsewhere at 1 year of age for malnutrition and again at the age of 6, when she had a chronic tracheobronchitis with a temperature of 104 F. A tentative diagnosis of celiac syndrome and pancreatic infantilism was made at that time. During the interval between admissions she averaged four stools a day but had eight large, foul, fatty stools when she included fats in her diet. She had a protuberant abdomen and moderate generalized adenopathy. The lungs were clear to percussion and auscultation. Laboratory examination revealed 4,210,000 erythrocytes and 69 per cent hemoglobin. The glucose tolerance curve was normal except for a rather low fasting sugar. Roentgenologic examination revealed pronounced increase in density of the right hilar shadow in the chest, opaque maxillary sinuses, and clouded ethmoid sinuses.



a. *b.* *c.*

FIG. 1. a. Large atonic colon filled with 1 gallon barium enema. b. Approximately 75 per cent expulsion of barium enema. c. Enlarged hilar glands and peribronchial infiltration.

Between her sixth and ninth years the patient averaged one to two stools daily but had constipation and pain just above the umbilicus. Her physician gave her liver injections and recommended a high protein, high carbohydrate, low fat diet.

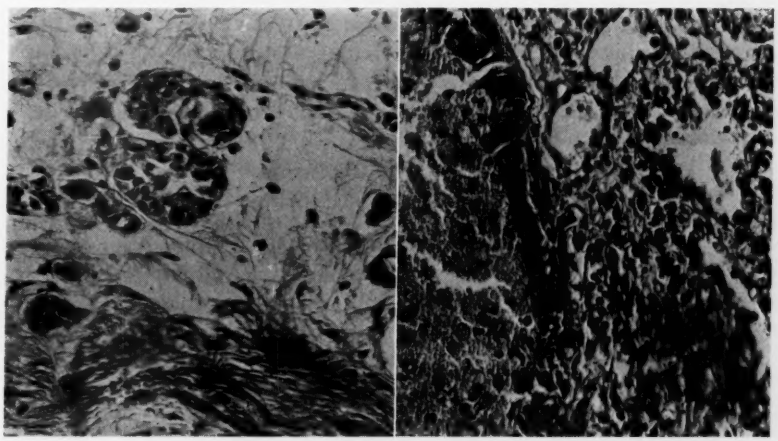
The child was admitted to the clinic at 9 years of age because of failure to gain weight, inability to digest food, attacks of abdominal pain, and a chronic morning cough. She was somewhat pale and had a rather protuberant abdomen. Her height was 49.5 inches and her weight 46 pounds. The tonsils were fairly large.

Chest examination revealed numerous moderately coarse, crepitant râles with increased breath sounds on the right to the fourth rib. A stereoroentgenogram revealed enlarged hilar glands and infiltration of the lungs (fig. 1c). The Mantoux test was negative, and no tubercle bacilli or fungi were found in three sputum specimens. No tubercle bacilli were found in the urine. The corrected sedimentation rate was 0.85 mm. per minute. Laboratory findings including blood calcium and blood phosphorus determinations were within normal limits.

Stool examination revealed numerous undigested meat fibers and slight increase in fatty acid crystals. Upon introduction of a 1 gallon barium enema a redundant atonic colon was found (fig. 1a). However, expulsion of 75 per cent of the barium was considered evidence against megacolon and was typical of celiac disease (fig. 1b).

During four months of observation the child's condition gradually became worse. Her temperature ranged from 100 to 101 F. daily, with increasing dyspnea and cough. At the last examination the right diaphragm was inactive.

The parents then took her to California, where she died suddenly about eight months after her first admission to the clinic. Postmortem examination was performed by Glen R. Halverson, M.D., of San Jacinto, California, who reported edema of the intes-



a. *b.*

FIG. 2. a. Cystic atrophy and fat infiltration. Almost total replacement of the glandular parenchyma by fatty tissue around normal islet tissue. b. Atypical bronchopneumonia with inflammatory infiltration. Bronchiole filled with purulent exudate.

tines and effusion of pleural, pericardial, and peritoneal cavities. The lungs were wet, and there was pus in the bronchioles. The pancreas was of average size, of lemon color, and cut as though it were fibrous tissue. Autopsy diagnosis was chronic bronchitis, metastatic calcification in kidneys, apparent congestive failure and cystic fibrosis of the pancreas.

C. S. Small, M.D., of Loma Linda, California and Harry Goldblatt, M.D., of Western Reserve University School of Medicine examined microscopic sections and agreed on the diagnosis of cystic fibrosis of the pancreas, although Dr. Goldblatt believed the case better called 'cystic atrophy and fat infiltration of the pancreas,' because there was no actual fibrosis in any of the sections examined (fig. 2a and b).

Because cystic fibrosis of the pancreas is a familial disease, it is important to note that a sister of the patient died of a similar disease at a much earlier age.

COMMENT

Although the celiac syndrome, or Gee-Herter disease, has been known since 1888, the first pathologic studies revealing the coexistence of fibrotic changes in the pancreas and the celiac syndrome were reported by Landsteiner[1] in 1905 under the heading of pancreatitis. In 1913 Garrod and Hurtley[2] reported a case of "congenital family steatorrhea," only one of two brothers having been observed. In 1925 Wolbach and Howe[3] demonstrated the presence of bronchiectasis in a high percentage of vitamin A deficient rats. In 1929 Kornblith and Otani[4] stated that both their reported case and that of Landsteiner represented inspissation of meconium into the pancreatic ducts, thus suggesting another possible cause for pancreatic fibrosis. In 1930 Harper[5] suggested that split fats in feces in celiac syndrome would differentiate the condition from pancreatic steatorrhea, because he thought that absence of pancreatic lipase resulted in unsplit fats in feces. This method of differentiation has been found unreliable, possibly because lipase of intestinal juice performs this function. In 1937 Sinclair and Smith[6] stated that fats are not absorbed until fatty acids undergo phosphorylation. Possibly exocrine pancreatic secretion is important in bringing about this phosphorylation, and therefore important in cystic fibrosis of the pancreas. In 1933 Ralli and others[7] demonstrated that pancreatectomized dogs fail to absorb vitamin A properly, a fundamental factor possibly related to the failure to absorb and utilize fats and in the production of symptoms and pulmonary changes in this disease.

Articles by Anderson[8], Thomas and Schlutz[9], and Harper[10] in 1938 pointed out the fact that some cases diagnosed celiac syndrome were actually cystic fibrosis of the pancreas. However, both conditions have many symptoms in common. In each the patient is young, usually has retarded physical development, passes large, foul, pale stools with intermittent diarrhea, and has a distended abdomen. According to Andersen[8], "Cystic fibrosis of the pancreas is a disease entity which

produces the celiac syndrome when the children survive the first year of life."

In 1939 Rauch and others[11] concluded that the pancreatic and pulmonary lesions are independent, but that they arise from a common congenital anomaly of the lungs and pancreas. In 1940 Cole and Howe[12] discussed six cases in adults of fatty liver with pancreatic atrophy. They considered these cases in adults to be similar to pancreatic fibrosis in children and pointed out that 60 per cent of Andersen's older group had fatty liver. They stated that it takes several weeks or months for pancreatic deficiency to produce a fatty liver. Experimental evidence indicates that survival and even weight gain are possible when only 10 per cent of pancreatic function is maintained.

The cause of this disease is not known, but Andersen[13] discussed (1) congenital defects, (2) inflammation of the pancreas in fetal life, and (3) vitamin A deficiency as possible causes. Atresia or even pseudoatresia of the pancreatic ducts[14,15], metaplasia of endothelial tissue in association with vitamin A deficiency, deposition of calcium in the pancreas, and the relative importance of disturbed metabolism have been discussed in recent years without the establishment of any definite etiologic factor. Snelling and Erb[16] recently queried whether vitamin A deficiency in the mother before childbirth might not be of etiologic importance.

The incidence may be as high as 3.3 per cent, reported by Andersen[8] in a careful survey of 605 microscopic sections of the pancreas at Babies Hospital in New York. That it is a disease of infancy is evidenced by the fact that 24 of her 49 patients died before 6 months of age. Andersen's oldest survivor lived until the age of 14½ years; the oldest of the 18 patients recorded by Menten and Middleton[17] was 10 years old. The patient presented in this article died at the age of 9.

That there is a strong familial tendency is demonstrated by our own patient, by Andersen (36 of 49 patients), and by Felsen and others,[18] who reported 4 instances with necropsy studies and 16 probable instances up to 1943. There seems to be no racial or economic group predilection, but 67 per cent of Andersen's patients were girls. We estimate that approximately 160 cases have been recorded to date.

Diagnosis. Although clinical diagnosis is difficult, differentiation of cystic fibrosis of the pancreas and the celiac syndrome has been made several times since 1938. Andersen said: "At present the differential diagnosis can be made with certainty only by examination of the duodenal juice for pancreatic enzymes or by microscopic examination of the pancreas. The best available proof of the diagnosis is the absence of

pancreatic trypsin and lipase in the duodenal juice." However, associated lesions such as chronic cough and roentgenologic evidence of bronchopneumonia or atypical pneumonia and occasionally bronchiectasis may suggest the possibility of pancreatic fibrosis. Chest symptoms may be the only or the primary presenting complaints. In a case reported by Mallory[19] chest lesions progressed from pneumonia, beginning with intersitial involvement of alveolar walls and peribronchial regions, to bronchiolectasis and bronchiectasis. Dilated bronchi and bronchioles become filled with purulent material caused by streptococci and secondary invaders such as staphylococci. Finally emphysema, atelectasis, and widespread lung fibrosis complicate the picture. A vitamin A tolerance test usually reveals a poor response both in cystic fibrosis of the pancreas and in the celiac syndrome. Attwood and Sargent[20] suggested that roentgenologic findings were in all lobes, as would be expected in a systemic disorder such as a vitamin A deficiency, but were more intense in the hilar regions. They also found disturbed intestinal motility and dilated loops of intestine with an occasional fluid level.

Fatty replacement of the pancreatic acinar parenchyma present in this case was observed in only 4 of Andersen's 49 cases. Dr. Small reported occasional spots of calcification in the epithelial linings of the kidney tubules of our case, a finding first recorded by Kennedy and Baggenstoss.[21] This may indicate some disturbance in the metabolism or excretion of calcium salts.

Salient differential points in distinguishing cystic fibrosis of the pancreas and the celiac syndrome have been compiled in the following table:

TABLE

CYSTIC FIBROSIS OF THE PANCREAS	Characteristics in Common	CELIAC SYNDROME
Familial tendency		
Onset usually in first year (insidious)		Onset rarely in first year
	Developmental retardation	
	Distended abdomen	
	Deficiencies: caloric, vitamin, and mineral	
Bulky stool (unsplit fat) Foul odor (putrefaction)	Diarrhea and constipation	Bulky, foul, and pale stool Frothy (fermentation)
Duodenal drainage Absent pancreatic enzymes		Normal
Abnormal x-ray of chest		Normal
Pathologic section, pancreas and lung, abnormal		Normal

Treatment. Because the disease is fatal, treatment is supportive. To supplement deficient pancreatic exocrine enzymes, pancreatin, lipocaic, or crude pancreatic extracts may be given in suitable quantities. In an attempt to limit metaplasia, vitamin A is given both orally and subcutaneously in therapeutic doses. Andersen suggested mother's milk and cod liver oil for infants in their first few months of life and the subsequent use of a high carbohydrate, high protein, low fat diet with caloric intake above the average requirement according to age.

SUMMARY

This case of cystic fibrosis of the pancreas reported with roentgenologic and necropsy findings was unusual in that the pancreatic acinar tissue was largely replaced with fat rather than fibrous tissue and that the patient lived an unusually long time. The disease was characterized by insidious onset of developmental retardation, diarrhea or bulky foul stools, and chronic respiratory infection. Although no clinical or pathologic studies were made on the patient's older sister, she reputedly died of a similar condition.

In infants with a feeding and developmental problem and an associated chronic pneumonic process or bronchiectasis, cystic fibrosis of the pancreas should be considered in the differential diagnosis.

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CYSTIC HYGROMA

Report of Three Cases

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Cystic hygroma is a benign disfiguring tumor of the neck, axilla, or chest wall and is thought to originate in anomalous development of the lymphatic system. Although the term *cavernous lymphangioma* is sometimes used, *hygroma*, derived from the Greek and meaning "moist tumor," is preferred.

EMBRYOLOGY

According to Jordan and Kindred[1] the lymphatic system develops in one of the two following ways:

"There has long been a question as to whether the lymphatic channels of the embryonic body develop as centrifugal endothelial sprouts from existing venous channels or by the fusion of isolated mesenchym-lined spaces, which upon fusion grow centripetally and transitionally

communicate with veins, particularly the subclavian, sciatic, and renal veins."

In a discussion of these two views it is stated:

"The alternate view, namely, that the lymphatic primordia develop from venous sprouts, is based largely on the work of Sabin. According to this view there appears in the embryo of the second month, vascular plexuses in connection with the subclavian, sciatic, and renal veins. These plexuses separate from their veins and become transformed into two paired and one unpaired lymph sacs and the unpaired retroperitoneal sac respectively. From these lymph sacs the sprouting lymphatics invade the body. The lymphatics of the head, neck, and arms grow from the jugular sacs; the lymphatics for the legs and trunk from the inguinal sacs; those for the mesentery from the retroperitoneal sac. Both views recognize the occurrence of these venous plexuses and the associated lymph sacs. According to the earlier view (Sabin) the venous plexuses become transformed into lymph sacs; according to the later view (Huntington and McClure) the lymph sacs arise in the extraintimal (perivenous) spaces of the disappearing venous plexuses. Only the jugular sacs acquire permanent venous connections. They serve to provide permanent openings into the internal jugular veins for the later thoracic duct on the left and the right lymphatic duct."

According to these views endothelial-lined channels or sacs give rise to sprouts, which extend centrifugally into surrounding tissues to form a lymphatic vascular system throughout the body. It is suggested that the cause of cystic hygroma may be accidental failure of some part of the lymphatic plexus derived from the jugular sacs to establish intercommunication with the venous system, with resultant segregation of primordial lymph channels. Endothelial cells of segregated lymphatic vessels form sprouts, which penetrate into surrounding tissues. But because of lack of communication with venous or other lymph channels, hygromatous cysts are formed. Endothelial lining cells of hygromatous cysts also send out sprouts to form new cysts and to secrete lymphoid material.

PATHOLOGY

As might be expected from this development, hygromas have a gross appearance of multilocular and multilobular cystic tumors. Depending upon their age individual cysts vary from less than a millimeter to several centimeters in diameter. Walls of small young cysts are delicate, thin, friable, and translucent, whereas those of old large ones are relatively thick, dense, and fibrotic. The cysts contain clear, straw-

colored, or serous lymphoid fluid. Within the tumor mass are varying amounts of degenerating muscle, fascia, fat, nerve filaments, and vessels, which have been engulfed during the growth and progressive penetration of lymphatic sprouts into adjacent tissues. No definite tumor capsule is formed.

Walls of individual hygromatous cysts are made up of one or more layers of endothelial cells. Supporting stroma in small cysts consists of a thin loose network of fine connective tissue fibers; stroma in large cysts has a large amount of dense fibrous tissue. Within the stroma are accumulations of lymphoid cells and in some areas hyperplastic lymph nodes.

DIAGNOSIS

Hygromas have a peculiar, rather characteristic, rubbery or spongy consistency on palpation. They often are lobulated and vary in size from small tumors to large masses. The skin overlying the tumor is freely movable, but because many tumors penetrate into surrounding tissues, especially muscles, the tumor mass may not be freely movable over underlying structures.

Hygromas usually occur in infancy or early childhood, although cases have been reported in which they did not appear until middle life. Symptoms are due principally to pressure. Protrusion into the floor of the mouth may interfere with deglutition; penetration into the mediastinum or the neck exerting pressure on the trachea may cause dyspnea; pressure on the cervical or brachial nerve plexus may cause pain, weakness, and paresthesia. Usually the tumors progressively enlarge, but regressions and almost complete but temporary disappearance have been observed.

Differential diagnosis. Hygromas should be considered in the differential diagnosis of tumors of the neck and axilla, especially in children. Pathologic conditions with which they may be confused are lymphadenitis, different types of lymphomas including Hodgkin's disease and lymphogenous leukemia, lipomas, simple or branchial cleft cysts, aberrant thyroid tissue or goiter, and metastases to lymph nodes. Hygromas involving the mediastinum resemble thymomas or other substernal tumors on roentgenologic examination, which should be made of all neck tumors.

TREATMENT

A comprehensive pathologic and clinical study of cystic hygromas was made by Goetsch[2], who, as have many surgeons, stated that radical

resection is the treatment of choice. In some cases, however, operation may not be indicated or successful. Because these tumors are particularly susceptible to infection, the mortality rate is quite high. Infection in addition to hemorrhage is the principal cause of postoperative death. It is not always possible to remove completely hygromatous tissues involving or extending into the mediastinum. Some cases have benefited by roentgen or radium irradiation.

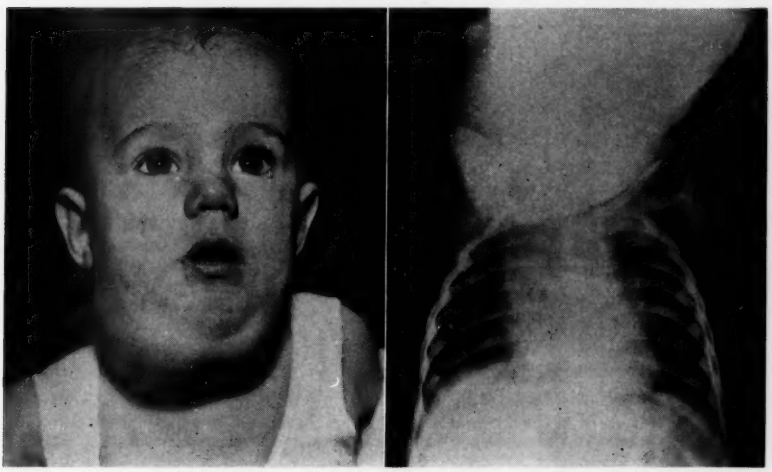
We have seen 7 patients with hygroma at the clinic, of which 3 are of particular interest and will be reported briefly to illustrate results of operation and irradiation.

CASE REPORTS

Case 1—A baby girl, aged 10 months, had progressively enlarging masses on either side of the neck below the mandible. The masses were pressing into the floor of the mouth (fig. 1a). The inside of the mouth had been incised at the age of six weeks without benefit. She had dyspnea and difficulty in taking nourishment.

The masses in the neck were lobulated and elastic but were not freely movable. The overlying skin was normal and movable. Roentgenograms of the chest showed a substernal mass (fig. 1b). Except for the tumor masses and undernourishment, physical and laboratory findings were normal.

The clinical diagnosis was cystic hygroma of the neck and mediastinum.



a. *b.*

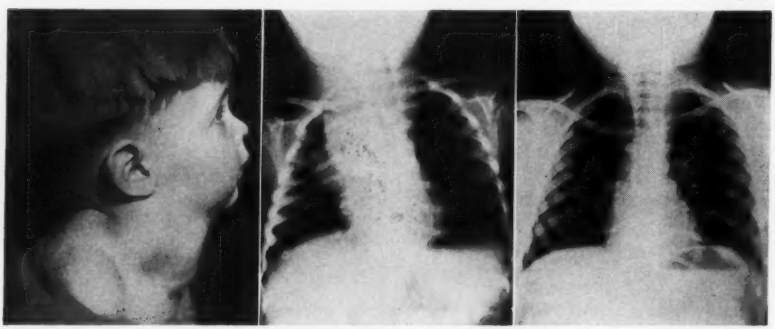
Fig. 1. a. Photograph showing bilateral involvement of neck. b. Roentgenogram of chest showing involvement of mediastinum.

A trial of roentgen therapy was advised. The technical factors employed were 200 kv., filter equivalent to 0.9 mm. hvl. copper, 50 cm. focus, skin-distance. Each side of the neck and the upper anterior mediastinum were given 100 r., measured on the skin through portals 10 by 10 cm. square, weekly for six weeks. The cervical masses began to diminish in size. When she returned for further treatment, the child had a fever, which followed vaccination a week previously, and it was decided to defer treatment until the fever subsided.

A few weeks later the child was taken elsewhere to a surgeon who attempted to remove the tumors in spite of extensive, surgically inaccessible, mediastinal involvement. The child recovered from the initial operation on one side of the neck. Later a second and more radical operation was attempted on the other side, and uncontrollable hemorrhage resulted in immediate death. The pathologist's diagnosis was "cystic lymphangioma."

Case 2—A baby boy, aged 2, was born with a cyst the size of a walnut on the right side of the neck. During the first year the tumor did not increase in size or cause symptoms. Then after a blow on the neck the cyst enlarged rapidly for about two weeks, and although it remained stationary, increasing dyspnea occurred. A roentgenogram of the chest revealed a substernal mass thought to be persistent thymus. A small amount of roentgen therapy was given to the neck and mediastinum. The tumor in the neck disappeared temporarily but soon returned to its original size, and a second treatment was given without benefit.

Physical examination of the child on admission revealed a large, lobulated, cystic mass in the right side of the neck extending from left of the midline anteriorly to the border of the trapezius muscle posteriorly (fig. 2a). The cyst was infected and was draining. Roentgenograms of the chest showed a substernal mass connected to the tumor in the neck (fig. 2b).

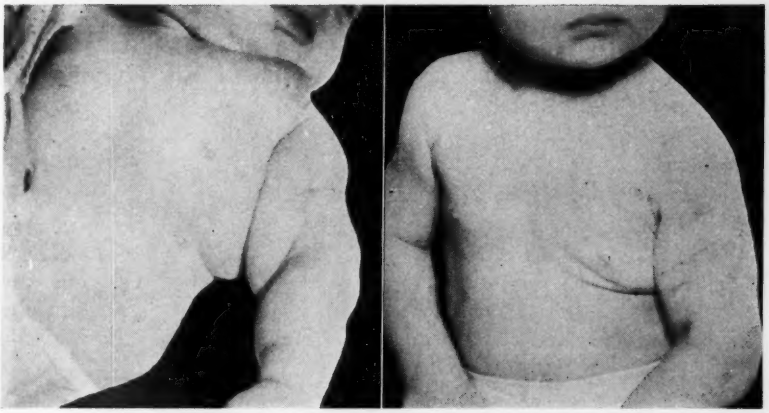


a. *b.* *c.*

FIG. 2. a. Photograph showing right side of neck. b. Roentgenogram of chest showing involvement of mediastinum. c. Roentgenogram of chest five years after implantation of radon seeds seen in right neck and upper mediastinum.

A diagnosis of cystic hygroma was made and excision advised.

The infected area was incised and drained. At operation several weeks later the cyst was found to involve the carotid sheath and to extend high up, posterior to the trachea, and downward into the mediastinum in close proximity to the large vessels.



a. *b.*

FIG. 3. a. Photograph showing involvement of left neck, chest, axilla, and upper arm. b. Photograph eighteen months after beginning of roentgen therapy shows considerable improvement.

Because it was impossible to resect all the mass, 14 radon seeds, each 1.4 mc. (filter 0.3 mm. gold), were implanted in the tumor remnants in the neck and mediastinum (fig. 2c). The pathologist reported the tumor to be cystic hygroma. Infection occurred after operation, but the child recovered and had no recurrence in nine years.

Case 3—A baby girl, aged 5 weeks, was born with "puffiness" of the left side of the neck, arm, and lateral chest wall. A diagnosis of sarcoma was made before her admission to the clinic. She was referred for roentgen therapy.

Examination revealed lobulated tumor masses filling the left supraclavicular fossa and axilla and extending down to the elbow and over the entire chest wall from sternum to axilla (fig. 3a). The rubbery consistency of the masses was characteristic of cystic hygroma. The skin was normal over the tumors, which were quite movable in some areas but somewhat fixed in others. The child was otherwise normal. Roentgenograms of the chest did not show mediastinal extension.

A clinical diagnosis of cystic hygroma was made.

After consultation with two surgeons who considered operation inadvisable because of extent of involvement, roentgen therapy was instituted. The technical factors used were the same as for the other cases. Through varying sized portals, different areas were given 100 r as measured on the skin at weekly and later monthly intervals for approximately two years. As nearly as it can be estimated, each part of the tumor mass received approximately 1200 r during this time.

Progressive reduction in size of all tumor masses occurred (fig. 3b). Only remnants remained above the elbow. At 2½ years of age the child was normally developed without apparent interference with bone growth or muscle function.

SUMMARY

Three cases of cystic hygroma, a benign tumor thought to originate in anomalous development of the lymphatic system, are reported. One operative death was caused by uncontrollable hemorrhage. The second patient, treated by operation and implantation of radon seeds in surgically inaccessible remnants of the tumor, had no recurrence in nine years. The third patient, treated by roentgen irradiation, improved symptomatically, and the tumor masses were reduced.

Hygroma is usually detected in infancy or early childhood, although occurrence in middle life has been reported. Symptoms are caused by pressure on adjacent structures, since the common sites are the neck, axilla, and chest wall. Differential diagnosis is sometimes difficult, and roentgenologic examination is necessary.

Surgical resection has been considered the treatment of choice, but the mortality rate is high, hemorrhage and infection being the principal causes of postoperative death. When surgical removal of all tumor tissue is impossible, patients have benefited by irradiation.

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